Impact of Extended Spectrum Beta-Lactamase Producing *Klebsiella pneumoniae* Infections in Severely Burned Patients

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BACKGROUND: Significantly higher mortality has been demonstrated in patients who suffer severe burns complicated by *Klebsiella pneumoniae* bacteremia. The specific virulence mechanisms associated with this organism in this population are unclear.

STUDY DESIGN: Our study assessed the impact of the mechanism of antibiotic resistance, strain clonality, and other host factors on morbidity and mortality. All patients with thermal burns infected with *K pneumoniae* between January 1, 2004 and July 1, 2008 were included in the analysis.

RESULTS: Ninety-one patients had 111 episodes of *K pneumoniae* infections, with 59 isolates among the 91 patients producing extended spectrum beta-lactamase (ESBL). Patients with ESBL-producing strains were slightly younger, had higher Injury Severity Scores (ISS), and higher percent full thickness burns. Those who survived to discharge were younger ($p < 0.001$), had less burned surface area ($p = 0.013$), had fewer ventilator days ($p = 0.016$), and fewer infections with ESBL-producing isolates ($p = 0.042$). Logistic regression revealed that an infection with ESBL-producing *K pneumoniae* during the hospital stay was the factor most predictive of death, with a nearly 4-fold increased odds of dying. However, survival duration analysis of the population with and without ESBL-producing *K pneumoniae* using Kaplan-Meier technique showed no significant difference in the populations. Cox regression proportional hazards model revealed that only age ($p = 0.01$) and ventilator days ($p \leq 0.01$) were associated with time to death. No specific clonality of the strains tested or ESBL production resistance genes were associated with mortality or ESBL production.

CONCLUSIONS: These results suggest that infections caused by ESBL-producing *K pneumoniae* are predictive of death when occurring in an older, more badly burned population. (J Am Coll Surg 2010;211: 391–399. © 2010 by the American College of Surgeons)

Klebsiella pneumoniae is an important pathogen that can cause severe infections in immunocompromised hosts with significant underlying disease.[1] As a nosocomial pathogen, it produces 3% to 17% of all bacterial infections.[1] Unfortunately, *K pneumoniae* frequently contains plasmid-encoded extended spectrum beta-lactamase (ESBL)-producing genes, which are associated with multidrug resistance. These multidrug resistant isolates are increasingly common in the setting of extensively used broad spectrum antibiotics, accounting for at least 20% of pathogenic isolates of *K pneumoniae* in 2003.[2] Infections caused by ESBL-producing *K pneumoniae* are associated with higher mortality when compared with non-ESBL-producing isolates, but the exact reason for this is unclear.[2,3]

A recent study involving patients with severe burns admitted to the burn center at the US Army Institute of Surgical Research/Brooke Army Medical Center demonstrated significantly higher mortality in burn patients with

Disclosure Information: Nothing to disclose.

Received February 6, 2010; Revised March 31, 2010; Accepted March 31, 2010.

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Published by Elsevier Inc.

ISSN 1072-7515/10/$36.00
doi:10.1016/j.jamcollsurg.2010.03.030

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01 SEP 2010	**N/A**	**-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Impact of extended spectrum beta-lactamase producing Klebsiella pneumonia infections in severely burned patients	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Bennett J. W., Robertson J. L., Hospenthal D. R., Wolf S. E., Chung K. K., Mende K., Murray C. K.,	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)	8. PERFORMING ORGANIZATION REPORT NUMBER
United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a REPORT	b ABSTRACT	c THIS PAGE			
unclassified	**unclassified**	**unclassified**	**UU**	**9**	

K pneumoniae bacteremia compared with bacteremia with methicillin-resistant *Staphylococcus aureus* (MRSA), *Acinetobacter baumannii,* and *Pseudomonas aeruginosa*.[4] Although there are multiple potential explanations for this difference, it has been suggested that the most likely are delays in the initiation of effective antibiotic therapy, mechanisms of antibiotic resistance, or highly virulent strains.[5] Because of the broad spectrum antibiotic resistance found in these isolates, carbapenems are the treatment of choice. Due to the high frequency of infections from ESBL-producing *Enterobacteriaceae* in our burn unit, clinicians empirically treat patients with a carbapenem in the setting of sepsis while awaiting culture and antimicrobial susceptibility data. Because this is the drug of choice for these infections, it is unlikely that initial inappropriate antimicrobial therapy accounts for the difference in mortality noted in our burn patients.[6]

Clinical risk factors are well described in patients with nosocomial *K pneumoniae* bloodstream infections. These include previous antibiotic use, both appropriate and inappropriate, and the use of extended spectrum cephalosporins, presence of indwelling lines and catheters, severity of illness, and corticosteroids.[7] Infections with ESBL-producing isolates also have specific risk factors that have been noted: age, length of hospitalization, and previous antibiotic therapy.[8] Previous studies describing the impact of *K pneumoniae* on mortality have been limited in several regards. First, most have focused primarily on patients with bloodstream infections and have not included patients with wound or respiratory infections.[5] Second, studies describing risk factors have been made up of primarily patients in intensive care units lacking populations of burn patients.[2,3,5,6,8] This study uses molecular biology techniques to determine ESBL types and strain variability and examines the presence of host factors to determine their potential role in morbidity and mortality during infections caused by ESBL-producing *K pneumoniae* in this population.

METHODS

Patient population

The US Army Institute of Surgical Research Burn Center is a 40-bed unit, located within Brooke Army Medical Center, that serves Department of Defense beneficiaries worldwide and the civilian population from within the southern Texas regional trauma system. Standard care for those with burns includes early burn wound excision and skin grafting, bronchoscopy within 24 hours of admission if there is a suspicion of inhalational injury, delivery of perioperative antimicrobials including vancomycin and amikacin, application of broad spectrum topical antimicrobials such as mafenide acetate, silver nitrate, and silver sulfadiazine at the discretion of the attending physician, and implementation of aggressive infection control. Bacterial cultures to diagnose infections were obtained at the discretion of the attending physician as clinically indicated, with routine surveillance cultures not obtained during the period examined in this study.

Study design

After institutional review board approval was obtained, an electronic retrospective chart review was performed to identify patients with burns admitted to the burn intensive care unit and infected with *Klebsiella pneumoniae,* between January 1, 2004 and July 1, 2008. Comparisons were made between patients with infections caused by ESBL versus non-ESBL–producing isolates. Each patient identified as having an infectious episode with *Klebsiella pneumoniae*, using previously established definitions,[8,9] was included only once for analysis. Mortality measures included all-cause in-hospital mortality at 7, 14, 21, and 28 days; morbidity was compared in terms of length of ICU stay, length of hospital stay, skin graft failure (when relevant), and other clinically relevant factors such as ventilator days. Inadequate antibiotic management was defined as greater than 48 hours between the time of culture and initiation of treatment using an antimicrobial to which the *K pneumoniae* isolate was ultimately determined to be susceptible in vitro.[5]

Characterization of *Klebsiella pneumoniae* clinical isolates

Available *K pneumoniae* clinical isolates were further tested to identify clonality and resistance mechanisms. Screening for ESBL-producing isolates was performed by the Brooke Army Medical Center clinical laboratory according to laboratory standard operating procedures using VITEK and VITEK2 (bioMérieux Vitek). Those isolates identified by the microbiology laboratory as likely to produce ESBL enzymes were further typed to identify the following specific classes of ESBL enzymes: CTX-M, SHV, and TEM.[9-11] Ertapenem susceptibility was used as the screening assay to identify *K pneumoniae* carbapenemase (KPC)-producing isolates. Because it is also possible that the combination of an AmpC type or extended spectrum beta-lactamase together with decreased porin expression on the bacterial cell surface can have a similar phenotype, molecular techniques were used for definitive identification. Published polymerase chain reaction primers were used to amplify bla_{KPC} gene products (KPC types 1 to 4), which were then compared with published sequences in the NCBI BLAST program database.[12,13]

The genetic relatedness of available isolates was compared by pulsed-field gel electrophoresis (PFGE) using

Table 1. Characteristics of Patients Infected with *Klebsiella pneumoniae* Based on Presence of Extended Spectrum Beta-Lactamase Production

Characteristic	ESBL present (n = 59)	ESBL absent (n = 33)	p Value
Age, y, median (range)	25 (19–85)	34 (13–80)	0.025
Male gender, n (%)	56 (95)	26 (79)	0.032
Median Injury Severity Score (range)	29 (1–75)	25 (4–50)	0.009
Median total body surface area burn, % (range)	47 (1–95)	34 (1–86)	0.141
Median full thickness burn, % (range)	33 (0–95)	15 (0–76)	0.024
Inhalation injury, (%)	26 (44)	11 (33)	0.314
Duration from burn to infection, d, median (range)	11 (2–217)	13 (2–100)	0.282
Source of infection, n (%)			0.087
Pulmonary	26 (44)	12 (36)	
Blood	23 (39)	17 (52)	
Urine	0 (0)	2 (6)	
Wound	10 (17)	2 (6)	
Mortality, n (%)	28 (48)	11 (33)	0.189
Time from infection to death, d, median (range)	30 (0–264)	53 (7–92)	0.628
Death <7 d, n (%)	5 (18)	1 (9)	0.655
Death <14 d, n (%)	9 (32)	2 (18)	0.461
Death <21 d, n (%)	11 (39)	3 (27)	0.713
Death <28 d, n (%)	14 (50)	3 (27)	0.288
Interventions, n (%)			
Foley catheter	58 (98)	33 (100)	1.00
Central venous catheter	57 (97)	30 (91)	0.346
Arterial line catheter	54 (92)	28 (85)	0.486
Median ventilator days (range)	4 (0–26)	3 (0–101)	0.613
Corticosteroids administered, n (%)	2 (3)	0 (0)	0.535
Glycemic control achieved, n (%)	11 (19)	6 (18)	0.954
Antibiotic effects, n (%)			0.197
Inappropriate coverage	5 (9)	0 (0)	
Delayed coverage	5 (9)	2 (6)	

ESBL, extended spectrum beta-lactamase.

Xba I restriction enzyme (New England Biolab). Pulsed-field patterns were analyzed and compared using commercial software (BioNumerics, Applied Maths Inc). PFGE patterns were grouped according to the Centers for Disease Control guidelines.[14] Isolates found to be indistinguishable, closely, and possibly related were grouped together and typed.

Statistical analysis

Differences in patient characteristics based on presence or absence of ESBL production were first analyzed, with each subject included once in the analysis and then again with every infectious episode coded as a separate event. Because results were similar between the 2 analyses, results from the individual patient episodes were reported. The means of the demographic characteristics of these 2 populations were compared by univariate analyses as appropriate. Student's *t*-test was used to evaluate normally distributed continuous variables, Mann-Whitney U test was used on non-normally distributed variables, and chi-squared test was used for categorical variables. Values of $p < 0.05$ were considered statistically significant.

Similarly, characteristics of patients who either survived or did not survive were compared via univariate analysis as appropriate. This analysis was performed twice, first with each subject included separately, and second, with each infectious episode included separately. As above, the results were similar and data are presented by each subject. To create a model to predict survival of patients infected with *K pneumoniae*, any characteristic with a p value < 0.1 was brought forward into the logistic regression. The model was controlled for the presence of EBSL-producing *K pneumoniae* at any time during the hospital stay. Variables were entered into the logistic regression in a backward Wald fashion. To temporally evaluate the impact of infections caused by an ESBL-producing isolate on subjects' deaths,

Table 2. Comparison of Survivors' and Nonsurvivors' Characteristics in Severe Burn Patients with *Klebsiella pneumoniae* Infections

Characteristic	Survivors (n = 53)	Non–survivors (n = 39)	Univariate p value	Multivariate p value	Odds ratio (95% CI)
Age, y, median (range)	25 (13–67)	31 (19–85)	0.034	0.001	1.08 (1.03–1.12)
Male gender, n (%)	46 (87)	36 (92)	0.509		
Extended spectrum beta-lactamase (ESBL), n (%)	31 (58)	28 (72)	0.189	0.042	3.45 (1.05–11.34)
Median Injury Severity Score (range)	25 (9–75)	29 (1–75)	0.231		
Total burn surface area, median % (range)	35 (1–95)	51 (1–95)	0.061	0.013	1.03 (1.01–1.05)
Full thickness burn, median % (range)	20 (0–95)	37 (0–90)	0.058		
Inhalation injury, n (%)	20 (38)	17 (44)	0.571		
Burn to infection, d, median (range)	11 (2–217)	12 (2–160)	0.890		
Source of infection, n (%)			0.065	0.030	1.80 (1.06–3.05)
Pulmonary	23 (43)	15 (39)			
Blood	25 (47)	15 (39)			
Urine	2 (4)	0 (0)			
Wound	3 (6)	9 (23)			
Bacteremia onset before 28 d, n (%)	5 (9)	10 (26)	0.115		
Polymicrobial, n (%)	13 (25)	17 (44)	0.054		
Acinetobacter baumannii	4 (8)	5 (13)			
Pseudomonas aeruginosa	2 (4)	8 (21)			
Methicillin-resistant *Staphylococcus aureus*	2 (4)	1 (3)			
Median ventilator days (range)	1 (0–40)	7 (0–101)	0.003	0.016	1.07 (1.01–1.13)
Corticosteroids administered, n (%)	0 (0)	2 (5)	0.177		
Glycemic control achieved, n (%)	9 (17)	8 (21)	0.666		
Antibiotic effects, n (%)			0.438		
Inadequate antibiotic coverage	4 (8)	1 (3)			
Delayed antibiotic coverage	3 (6)	4 (10)			

the logistic regression was also performed to predict characteristics of survivors and nonsurvivors using time points of 7, 14, 21, and 28 days after initial infection.

Survival of subjects with and without ESBL-producing *K pneumoniae* was analyzed using the Kaplan-Meier survival technique. Time to survival endpoints were calculated using the date of the initial culture from which *K pneumoniae* was isolated and ended when a patient either died or was censored at discharge from the hospital. The log-rank test was used to test for differences in cumulative survival between the 2 populations. Cox regression was used to study the contributing factors in time to death of subjects infected with *K pneumoniae* and the results were calculated in hazard ratios. The variables of interest were entered in a backward Wald fashion and the model was controlled for presence of ESBL-producing *K pneumoniae* at any time during the hospital stay. The model also created separate survival curves based on ESBL status.

RESULTS

A total of 975 patients were admitted to the burn ICU during this period, with a median total body surface area burn of 10% (range 0% to 99%), median age 41years (range 11 to 101 years), median length of stay of 4 days (range 0 to 900 days), and mortality rate of 8.6%. Of the 975 admissions, 485 were admitted to the Burn ICU with a median total body surface area burn of 18% (range 0% to 99%), median age 44 years (range 11 to 101years), median ICU length of stay 3 days (range 1 to 427 days), and mortality rate of 17.1%.

Ninety-one patients had 111 episodes of *K pneumoniae* infection. Among the 91 patients, 59 had isolates that produced at least 1 ESBL (65%) (Table 1). The majority of patients had bloodstream infections. Slightly more patients infected with ESBL-producing strains had pneumonia; more non-ESBL–producing strains caused bloodstream infections. Patients with ESBL-producing strains were younger, had higher Injury Severity Scores (ISS), and higher percent full thickness burns. No difference was found in mortality, time to mortality, or duration of hospitalization for those with ESBL versus non-ESBL producing isolates. In addition, inadequate antimicrobial coverage or delay in time to antimicrobial coverage was not associated with infections by ESBL-producing isolates.

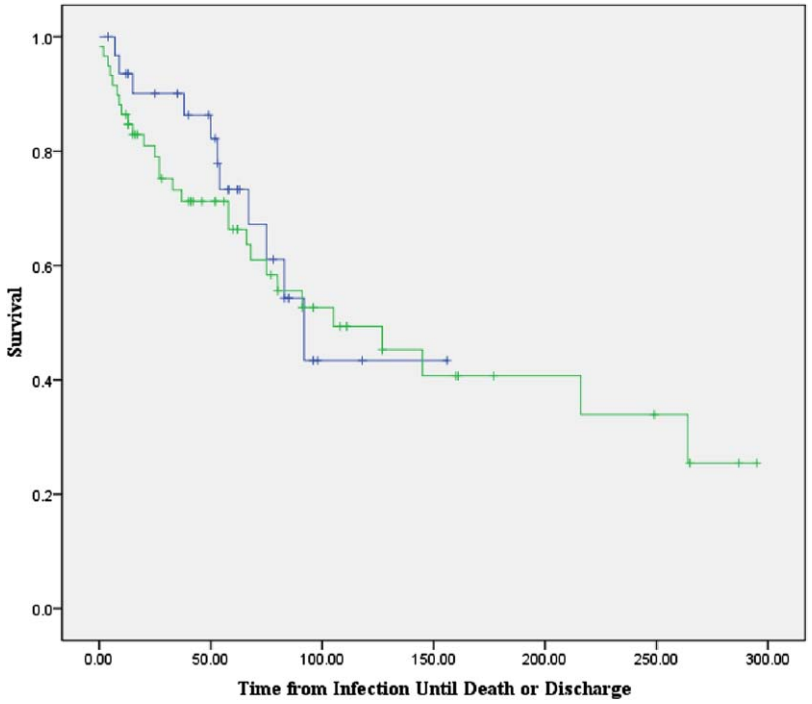

Figure 1. Kaplan-Meier survival curve comparing subjects infected with *Klebsiella pneumoniae* strains that are extended spectrum beta-lactamase (ESBL)-producing and non-ESBL producing strains. Green line shows ESBL present, blue line shows ESBL absent.

Evaluation of the characteristics of subjects with *K pneumoniae* infections who survived to discharge showed them to be younger ($p < 0.01$, odds ratio [OR] 1.08, 95% CI 1.03 to 1.12), and have less burned surface area ($p = 0.013$, OR 1.03, 95% CI 1.01 to1.05), fewer days on the ventilator ($p = 0.016$. OR 1.07, 95% CI 1.01 to 1.13), fewer infections with ESBL-producing isolates ($p = 0.042$, OR 3.45, 95% CI 1.05 to 11.34), as well as a greater proportion of pulmonary or bloodstream infections ($p = 0.03$, OR 1.89, 95% CI 1.06 to 3.05) (Table 2). Although there was no significance associated with source of infection between isolates with and without ESBL-production, there was a higher percentage of patients with ESBL-producing *K pneumoniae* in the wounds. Logistic regression revealed that the presence of an ESBL-producing isolate during the hospital stay was the factor most predictive of death, with a nearly 4-fold increased odds of dying. Although the analysis demonstrated that an infection caused by an ESBL-producing *K pneumoniae* at any time during the hospital stay was predictive of death, analyses attempting to show a temporal relationship between isolation of the organism in culture and death did not suggest a significant correlation. Analyses performed at 7, 14, 21, and 28 days after infection showed no statistically significant difference in the proportion of deaths in the ESBL positive and negative populations (data not shown).

Survival analysis of the populations with and without ESBL-producing *Klebsiella* using the Kaplan-Meier technique showed no significant differences (Fig. 1, log-rank test $p = 0.67$). Cox regression proportional hazards model was used to investigate the effects of several factors on time to death including age, days on ventilator support, total burned surface area, source of infection, and presence of polymicrobial infection. The factors that had an effect on time to death were age ($p = 0.01$, hazard ratio [HR] 1.01, 95% CI 1.00 to 1.01) and ventilator days ($p \leq 0.01$, HR 1.03 95% CI 1.01 to 1.04). Although not statistically significant, ($p = 0.16$, HR 0.60, 95% CI 0.30 to 1.2), the survival curves of subjects with and without ESBL-producing *K pneumoniae* did diverge, suggesting that an effect might have been present if there had been more episodes to include in the analysis (Fig. 2).

Thirty-eight strains were available for detailed analysis of PFGE patterns and resistance genes (Table 3). There were 23 different PFGE types with no clear association with outcomes by clonality. SHV was found in 37 (97%) of the strains tested while none of the strains contained CTX-M or the carbapenemase gene bla_{KPC}. TEM was present in 23

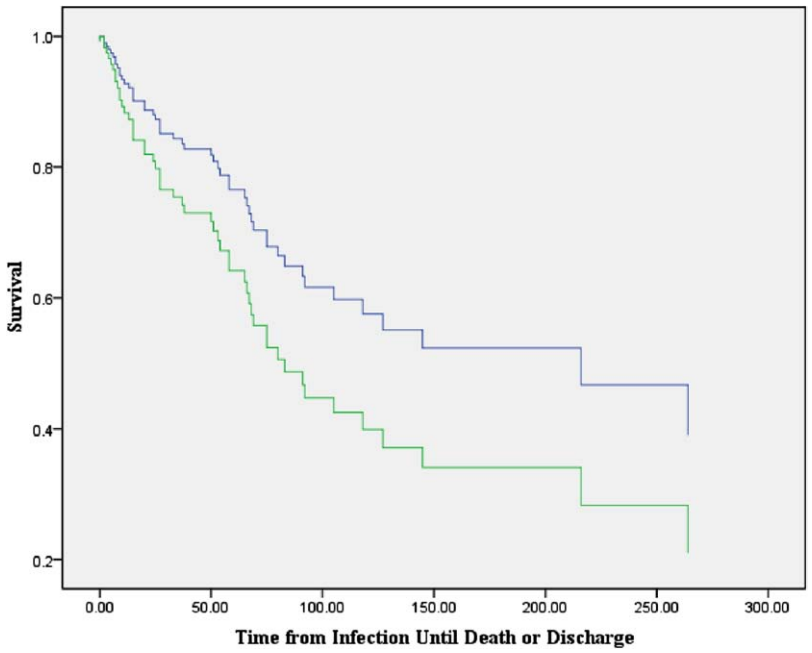

Figure 2. Cox regression model of contributing factors in time to discharge or death comparing subjects with and without extended spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* infections. Green line shows ESBL present, blue line shows ESBL absent.

(61%) isolates but was not consistently found over time or even within the same PFGE type strains. Strains with TEM were present during every year of the study.

DISCUSSION

ESBL-producing *K pneumoniae* are important pathogens that cause serious infections in hospitalized patients. These infections are often difficult to treat because the isolates are often resistant not only to beta-lactams, but also to aminoglycosides and fluoroquinolones. In a recent retrospective review at our institution, *K pneumoniae* bacteremia was found to be an independent risk factor associated with higher mortality in the burn unit compared with bacteremia caused by *Acinetobacter*, *Pseudomnas aeruginosa,* and methicillin-resistant *Staphylococcus aureus*.[4] Higher mortality was noted with *K pneumoniae* bacteremia regardless of total body surface area burn or Injury Severity Score, demonstrating the importance of this pathogen in our hospital.[4] Additionally, multidrug resistance was associated with mortality; however, the explicit cause of that mortality, including the role of ESBL production specifically could not be elucidated.

In this study, we expanded on the findings of the earlier study, further defining the clinical factors associated with mortality in patients admitted to the burn ICU, including a 4-fold increase in the odds of dying from infections caused by ESBL-producing *K pneumoniae*. A more detailed statistical analysis of the risks associated with mortality from infections caused by these isolates demonstrated associations with patients who were older, had higher total body surface area burned, with more ventilator days. There was no association between strain clonality and outcomes. In addition, the epidemiology of the evaluated mechanisms of resistance varied over time and did not appear to be associated with worse outcomes. An infection caused by an ESBL-producing *K pneumoniae* was predictive of mortality, with nearly a 4-fold increased risk compared with other clinical factors. When looked at independently by Kaplan-Meier analysis and when combined with other variables in a Cox regression, the presence of an ESBL was not significantly associated with time to death. However, the diverging survival curves of subjects with and without ESBL-producing organisms suggest that patients infected with ESBL-producing strains might have a more rapid time to death. Further attempts to temporally relate ESBL-producing isolates with death were also not statistically significant. Finally, inadequate or delayed use of appropriate antimicrobials did not appear to be associated with poor outcomes.

Taken together, these results suggest that infections caused by ESBL-producing *K pneumoniae* in an older, more severely burned population carry a higher risk of

Table 3. Pulsed-Field Gel Electrophoresis Types of *Klebsiella pneumoniae* Strains from Severely Burned Patients and Etiology of Beta-Lactam Resistance

Year of isolate	PFGE type	Clinical assessment of ESBL production	PCR			
			TEM	SHV	CTX	KPC
2006	Type 1 C	pos	neg	pos	neg	neg
2007	Type 1 C	pos	pos	pos	neg	neg
2007	Type 1 C	pos	pos	pos	neg	neg
2007	Type 1 C	pos	pos	pos	neg	neg
2007	Type 1 C	pos	neg	pos	neg	neg
2006	Type 2	pos	pos	pos	neg	neg
2006	Type 2	pos	pos	pos	neg	neg
2006	Type 2	pos	pos	pos	neg	neg
2006	Type 2	pos	pos	pos	neg	neg
2007	Type 2	pos	pos	pos	neg	neg
2008	Type 2	pos	pos	pos	neg	neg
2008	Type 2	pos	pos	pos	neg	neg
2008	Type 2 C	pos	neg	pos	neg	neg
2007	Type 3 C	pos	neg	pos	neg	neg
2007	Type 5	pos	pos	pos	neg	neg
2005	Type 6	pos	pos	pos	neg	neg
2007	Type 6	pos	pos	pos	neg	neg
2006	Type 10	pos	pos	pos	neg	neg
2006	Type 10	pos	pos	pos	neg	neg
2006	Type 16	pos	pos	pos	neg	neg
2008	Type 17	pos	pos	pos	neg	neg
2008	Type 17	pos	pos	pos	neg	neg
2005	Type 18	pos	pos	pos	neg	neg
2008	Type 18	pos	pos	pos	neg	neg
2007	Type 24	pos	pos	pos	neg	neg
2007	Type 25	pos	neg	pos	neg	neg
2006	Type 26	—	neg	pos	neg	neg
2007	Type 27	—	neg	pos	neg	neg
2008	Type 28	—	neg	pos	neg	neg
2006	Type 29	pos	pos	pos	neg	neg
2006	Type 33	—	neg	pos	neg	neg
2006	Type 36	—	neg	neg	neg	neg
2007	Type 39	—	neg	pos	neg	neg
2007	Type 39	—	neg	pos	neg	neg
2006	Type 40	—	neg	pos	neg	neg
2006	Type 43	pos	pos	pos	neg	neg
2006	Type 44	—	neg	pos	neg	neg
2007	Type 45	—	neg	pos	neg	neg

TEM, SHV, CTX, and KPC are ESBL enzymes.
ESBL, extended spectrum beta-lactamase; PCR, polymerase chain reaction; PFGE, pulsed-field gel electrophoresis.

death. The direct implication of these infections remains unclear because we could not establish a link between the timing of infection with ESBL-producing *K pneumoniae* and patient demise. It is possible that the presence of an ESBL-producing isolate is a marker of a "sicker" patient. These isolates are most likely nosocomially acquired during frequent contacts with hospital staff because of the need for higher level wound care and other medical and surgical interventions. Conversely, previous studies have noted that ESBL-producing organisms are independently associated with increased mortality and this study may be underpowered to detect a difference in time to death that may exist. Assuming that the observed mortality rates would remain similar in a larger population, to have 80% power to detect

an actual difference with alpha set at 0.05, approximately 300 subjects would be required. Currently, this study contains approximately 30% power to detect a difference of 15% increase in mortality if one exists.

Previous studies, not specifically performed in burn patient populations, have demonstrated significant differences in hospital costs ($41,353 vs $24,902) and length of hospital stays (21 days vs 11 days) associated with infections from ESBL-producing isolates when compared with non-ESBL-producers.[6] More importantly, ESBL-producing *K pneumoniae* infections result in higher rates of treatment failure (31% vs 17%) and mortality (25% vs 11%) when compared with infections with non-ESBL-producing isolates.[8] Our study in this group corroborated those findings with regard to increased mortality. It is notable that patients in our study who were infected with ESBL-producing strains were typically younger males who generally have better outcomes than older females in severely burned populations.[15-19] This might be balanced out by the fact that the younger patients infected with ESBL-producing isolates had higher percentages of full thickness burns and higher Injury Severity Scores. In addition, the unique population under study here, in which effective antibiotic has become the standard empiric antimicrobial agent for patients in the burn ICU, allowed us to evaluate outcomes without the bias of inadequate therapy.[5,20] Overall, outcomes with bacterial infections in burn patients might be more significantly influenced by host factors to a greater degree than the specific bacterial strains or those strains' resistance patterns.

Our study is limited by its retrospective nature, but the ability to control for key variables generally linked to mortality and to test individual isolates for mechanisms of resistance allude to the continued role of host factors associated with mortality. In addition, there were a limited number of patients evaluated, and greater numbers might have enabled us to identify a relationship between ESBL-producing isolates and time to death. Studies that attempt to demonstrate associations between risk factors or interventions and outcomes in patients who suffer severe burns should ensure that host-specific factors are included in all analyses in order to detect true correlations. Finally, infections caused by ESBL-producing *K pneumoniae* should be treated aggressively in all burn patients, but particularly in older patients with more severe burns.

Author Contributions

Study conception and design: Bennett, Robertson, Hospenthal, Wolf, Chung, Mende, Murray

Acquisition of data: Bennett, Murray

Analysis and interpretation of data: Bennett, Robertson, Hospenthal, Wolf, Chung, Mende, Murray

Drafting of manuscript: Bennett, Robertson, Hospenthal, Wolf, Chung, Mende, Murray

Critical revision: Bennett, Robertson, Hospenthal, Wolf, Chung, Mende, Murray

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